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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,922	08/02/2001	Atsushi Miyawaki	11283-012001 / PH-1270US	7108
7590	08/06/2002			
CHRIS T. MIZUMOTO Fish & Richardson P.C. Suite 2800 45 Rockefeller Plaza New York, NY 10111			EXAMINER WHISENANT, ETHAN C	
			ART UNIT	PAPER NUMBER
			1634	
			DATE MAILED: 08/06/2002	9

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/920,922	MIYAWAKI ET AL.
	Examiner	Art Unit
	Ethan C. Whisenant, Ph.D.	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM  
THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) Responsive to communication(s) filed on 02 August 2001 .

2a) This action is **FINAL**.      2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4) Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5) Claim(s) \_\_\_\_\_ is/are allowed.

6) Claim(s) 1-9 is/are rejected.

7) Claim(s) \_\_\_\_\_ is/are objected to.

8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on \_\_\_\_\_ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some \* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_ .

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)  The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ .
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>7-8</u> .	6) <input type="checkbox"/> Other: _____ .

## DETAILED ACTION

**1.** The applicant's Preliminary Amendment has been entered. The applicant's Preliminary Amendment was filed on 02 AUG 01 and has been entered as paper no. 6 (Amdt. A). Following the entry of the Preliminary Amendments **Claim(s) 1-9** is/are pending.

### SEQUENCE Rules

**2.** This application now complies with the sequence rules and the sequences have been entered by the Scientific and Technical Information Center.

### 35 USC § 112- 2ND PARAGRAPH

**3.** The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

### CLAIM REJECTIONS under 35 USC § 112- 2ND PARAGRAPH

**4.** **Claim(s) 1-9** is/are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

**Claim 1** is unclear for a number of reasons. To begin, the second paragraph, which begins "a digestion in which..." is confusing, and, as a result, it is unclear as to what is to occur during this step. It appears the phrase "in which said step of DNA synthesis is repeated several times to amplify the DNA containing said primers" is misplaced. It appears that this phrase would make more sense if it were part of the first paragraph.

Also, the phrase "and, then, at least DNAs other than the amplified circular DNA are digested into several fragments" is confusing because it is unclear if the amplified circular DNA produced in the first paragraph (first step) is to be /can be digested. Based on Figure 1, and claim 6, it looks like both the methylated and hemi-methylated DNAs are both digested during the digestion step.

Finally, the phrase "as megaprimer" in the third paragraph (line 12 of Claim 1) is nonsequitur. Please clarify Claim 1.

**Claims 2 and 3** are confusing because it is unclear to which "DNA synthesis" step the claims refers, the first (i.e. step 1 – paragraph 1) or the second (i.e. step 3 – paragraph 3) or both. It appears that the first step is the DNA synthesis step while the third step is the double-stranded DNA synthesis step. This is how the claims have been interpreted in the prior art rejection(s) which follow.

### **35 USC § 103**

**5.** The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

**6.** This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

### **CLAIM REJECTIONS UNDER 35 USC § 103**

The following prior art rejection(s) is/are made in view of the ambiguity of the Claims and represent the examiner's best interpretation of the claimed invention.

**7. Claim(s) 1-4, 6-7 and 9 is/are** rejected under 35 U.S.C. 103(a) as being unpatentable over Stemmer et al. [US 5,811,238(1999)] in view of Bauer [US 5,789,166(1998)].

**Claim 1** is drawn to a method of mutagenesis which method is to comprise three steps. To begin, a DNA synthesis is performed in which one or more primers which have a nucleotide sequence containing at least one mutation and a phosphorylated 5'-terminus are annealed to a template DNA and then subjected to an elongation reaction using a thermostable high-fidelity DNA polymerase, after which the phosphorylated 5'-terminus and the elongated terminus are ligated by means of a thermostable

ligase to synthesize a circular DNA containing said primers. This DNA synthesis step is repeat several times to amplify the DNA containing said primers. Then, in the second step (i.e. the digestion step) the amplified circular DNAs are digested into several fragments. Finally, in the third step the several fragments generated during the digestion step are used as megaprimer to amplify the circular DNAs produced during the first step.

As the examiner reads it, the claimed invention it appears to be a combination of site-directed mutagenesis followed by a step wherein the megaprimer method of mutagenesis is carried out. Stemmer et al. teach DNA shuffling mutagenesis wherein the products (i.e. a circular DNA) of an earlier amplification process are digested to produce megaprimer. See Stemmer et al., at least for example, Column 7, lines 15-35 and note that Stemmer et al. teach a variation of their method wherein a step of site-directed mutagenesis is performed prior to their shuffling mutagenesis method - which is simply a modification of the megaprimer mutagenesis method. Also see Column 24, lines 44-59. The method of Stemmer et al., therefore, may include a step wherein site-directed mutagenesis is performed prior to DNA shuffling. Clearly, Stemmer et al. do not teach the type of site-directed mutagenesis outlined in steps 1-2 of the claimed invention. However, Bauer et al. do teach a method of site-directed mutagenesis (i.e. the Quick change site-directed mutagenesis method) which comprises all of the limitations present in the first two steps of the claimed invention. Therefore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to modify the method of Stemmer et al. wherein site-directed mutagenesis is performed prior to DNA shuffling. Furthermore, absent an unexpected result it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to use the site-directed mutagenesis method of Bauer et al. as the site-directed mutagenesis method. Note that there is no invention involved in combining old elements in such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955). Finally, the substitution of one known method with known properties for a second well known method with known properties would have been *prima facie* obvious to the ordinary artisan at the time of the invention in the absence of an unexpected result. As regards the motivation to make the substitution recited above, the motivation to combine arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making this obviousness rejection comes from the M.P.E.P. at 2144.07 and 2144.09.

**Claim 2** is drawn to an embodiment of Claim 1 wherein during said DNA synthesis step several of said primers are used to introduce mutations at multiple sites simultaneously. Both Stemmer et al. and Bauer et al. teach this limitation as part of their respective methods. See for example, Stemmer et al. Column 22, lines 60-67 and/or Claims 16-20. Also, see Bauer et al., Claim 1, wherein these authors teach using two (i.e. several) mutagenic primers to mutate the template DNA.

**Claim 3** is drawn to an embodiment of Claim 1 wherein during said DNA synthesis step degenerative primers are used to introduce random mutations at certain sites in a nucleotide sequence. Stemmer et al. teach this limitation wherein these authors teach using oligos of random sequence (i.e. degenerative primers) as primers in their method of mutagenesis. See for example, Stemmer et al. Column 22, lines 60-67.

**Claim 4** is drawn to an embodiment of Claim 1 wherein during said double-stranded DNA synthesis step an auxiliary primer complementary to a region adjacent to the nucleotide sequence in which mutations are introduced is added. Admittedly, neither Stemmer et al. or Bauer et al. explicitly teach adding an auxiliary primer complementary to a region adjacent to the nucleotide sequence in which mutations are introduced, however, this limitation is considered to be inherent to the method described by Stemmer in that they teach using random sequence primers which will hybridize to and therefore be complementary with a region adjacent to the nucleotide sequence in which mutations are introduced.

**Claim 6** is drawn to an embodiment of Claim 1 wherein during said digestion step methyhlated and hemi-methylated nucleotide sequences are selectively cut. Bauer et al. teach this limitation.

**Claim 7** is drawn to an embodiment of Claim 1 wherein during said digestion step DpnI is used. Bauer et al. teach this limitation.

**Claim 9** is drawn to an embodiment of Claim 1 wherein, in said step of DNA synthesis, the entire step is completed in a reaction solution comprising at least said primers, said template DNA, said thermostable high-fidelity DNA polymerase, and said thermostable DNA ligase. Bauer et al. teach this limitation.

#### CLAIM OBJECTIONS

**8.** **Claim(s) 5 and 8** is /are objected to - as related to the prior art – because they are dependent upon a rejected independent base claim.

#### CONCLUSION

**9.** **Claim(s) 1-9** is/are rejected and/or objected to for the reason(s) set forth above.

**10.** Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ethan Whisenant, Ph.D. whose telephone number is (703) 308-6567. The examiner can normally be reached Monday-Friday from 8:30AM -5:30PM EST or any time via voice mail. If repeated attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached at (703) 308-1152.

The fax number for this Examiner is (703) 746-8465. Before faxing any papers please inform the examiner to avoid lost papers. Please note that the faxing of papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989). Any inquiry of a general nature or relating to the status of this application should be directed to the group receptionist whose telephone number is (703) 308-0196.



**ETMAN C. WHISENANT**  
**PRIMARY EXAMINER**